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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/473,872	YOON, KYONGGEUN	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is an original application filed December 28, 1999.

Applicant's amendment filed August 27, 2003, has been received and entered. Claim 40 has been amended. Claims 43-53 have been added. Claims 40-53 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Newly amended claims 40-42 and newly added claims 43-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, in claim 40 the recitation of "lasting more than one hair cycle and leading to development of dark pigmented hairs" (claim 40), and in claim 43, the recitation an animal model that "is incapable of germline transmission" (claim 43) is considered new matter. The support for the recitation indicated by Applicant is noted (see Applicant's

amendment page 5, Section I), however, these portions of the specification do not provide literal support for the amendments. In each case, the support for the claim amendments comes from simple description of experiments performed in mice under specific delivery and experimental conditions. For example, at page 14, lines 5-18 it is acknowledged that providing a specific RNA-DNA to an albino mouse with a specific mutation altered the Tyr gene in the albino mouse resulting in pigmented hair, however this end point is not considered to be commensurate in scope with the method as instantly claimed. The instant claim encompasses practice in humans, correction of any Tyr mutation, and correction in cells that produce or do not produce hair of any color. Initially, upon review of the specification there is nothing at this passage nor anywhere else in the specification that indicates that the methods should be practiced in mice or humans were the hair should be "dark" and "pigmented" or that practice of the method was intended to change the characteristic of hair color. Further, there is nothing in the claim nor the specification that distinguishes the practice of the method such that performing the steps selectively results in alteration that last "for more that one hair cycle" for example from an alteration lasting less than one hair cycle, or an alteration lasting more than one cycle and not altering hair color. The portion of the specification pointed to by Applicant supports what is generally known about hair growth and development, and provides a basis for affects of transfecting specific types of cells in the skin with a specific mutation in the Tyr gene, but not the breadth of practicing the method as claimed. Similarly, for the animal models encompassed by claim 43 and dependent claims, there is no support for the full breadth of the claim. The limitation of "incapable of germline

transmission" is not fully supported by the present specification as being specifically contemplated to part of the claimed invention. Further, the term "incapable of germline transmission" broadly encompasses other limitations such as embryonic lethal animal models and immature animals incapable of sexual reproduction not specifically contemplated. While would Examiner acknowledge that making a mutation in a skin cell would probably not be transferred to the germline cells, however review of the specification indicates that the full breadth of "incapable of germline transmission" was not specifically contemplated nor does the specification provide the necessary teaching to make and use the claimed product in the full breadth as claimed.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 40-53 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to

include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure". In the instant case it does to appear that the specification provides adequate support for the limitations to the claimed invention as discussed above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 40 is unclear in the recitation of "leading to the development of dark pigmented hairs" because there is insufficient antecedent basis for this limitation in the claim. Upon review of the specification there is no teaching that the method must be practiced in an animal that produces dark hair, or that altering the Tyr gene with a Tyr-A oligo would produce dark hair in

such an animal. The metes and bounds of the claim are not adequately defined because it is unclear if the method can only be practiced in animals that have dark hair, or if the method practiced in an animal with any color hair must meet this limitation. Further, the term "dark" is not specifically defined in the specification, and the color or tone encompassed by this term is not adequately set forth to define the metes and bounds of practicing the method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 43, 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexeev *et al.* (IDS reference).

Newly added claim 43 is drawn to a product made by a particular process. More specifically the claims require that he resulting animal have a particular phenotype such as albinoism and that the animal model can not transmit the phenotype through the germline transmission. Dependent claims 46-48 encompass an albino animal with a mutation in the Tyr

gene. Thus, the claims broadly encompass an animal model having a skin disorder wherein the disorder comprises a mutation generated in a gene which leads to said disorder, and dependent claims are drawn to specific genes and specific types of mutations. Examiner notes that Alexeev *et al.* teach methods to correct a particular gene mutation in cells *in vitro*, however the cells for the study are isolated from an animal whose skin cells display the phenotype of albino melanocyte. Further, the albino mice used by Alexeev are young and not yet sexually mature. The basis of anticipation is that the young albino mouse which contains the specific point mutation which results in the albino phenotype. Therefore, the animals taught by Alexeev *et al.* represent an animal model for the study of a mutation in the Tyr gene.

Case law states that where the claimed and prior art products are identical or substantially identical in structure or composition, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Examiner conceded that the animal disclosed by Alexeev *et al.* are not made by the instantly claimed process, however the resulting animal containing a mutation which results in an albino phenotype would be indistinguishable from that disclosed in Alexeev *et al.* Case law states that a *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v.*

Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01. In the instant case, the instantly claimed animal model is presented as a product by process claim, however there is no evidence of record, nor has Applicant provided evidence that the albino mouse disclosed in Alexeev *et al.*, or any other animal containing a mutation which results in an observable phenotype, would be any different if it were generated by altering the genome of a normal mouse by using the instantly claimed method.

Thus, the animals containing a mutation in the Tyr gene as taught by Alexeev *et al.* represent an animal model which anticipates the instant claims.

Claims 43 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Jianmin (US Patent 6,596,924).

Newly added claim 43 is drawn to an animal model with a skin disorder including a keratinization disorder (claim 45) wherein the animal is incapable of transmitting a mutated gene through the germline. Jianmin teach a method of culturing HPV through the use of skin grafts on host animals (abstract and column 12, lines 42-56). Jianmin teaches that such skin grafts produce papillomas which among the various types formed and scored represent a skin disorder with dense keratinization (column 18, lines 1-8). Because HPV is fastidious in its culture requirement, the host animal containing the skin cell xenograft is not infected, and thus the

germline is not infected. Therefore, the animal model taught by Jianmin anticipates the animal model encompassed by the instant claims.

As discussed above, case law states that where the claimed and prior art products are identical or substantially identical in structure or composition, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Examiner conceded that the animal disclosed by Jianmin are not made by the instantly claimed process, however the resulting animal model containing HPV infected cells that produce hyper keratinized skin lesions are encompassed by the instant claims as made by a different process. Case law states that a *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

Thus, the animal model taught by Jianmin represent an animal model which anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-42 stand and newly added claims 43-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon *et al.* (PNAS, 1996), Alexeev *et al.* (Nature Biotech, 1998), Furth *et al.* (US Patent 5,998,382), Gilchrest *et al.* (US Patent 5,580,547) and Stout *et al.* (US Patent 6,319,224).

Applicant summarizes the specific teaching of each of the references and argue that there is no specific motivation to combine the teachings contained in the references themselves to combine the teachings of the references as a whole to arrive at the claimed invention. See pages 5-6. Further, Applicant argues that there is no motivation to practice the method *in vivo*, only *in vitro*. See pages 6-7. Furthermore, Applicant argues that there is no expectation of success, in particular noting the claims require alteration of a Tyr gene in a hair follicle cell, and that the genetic alteration affected by delivery of the Tyr-A oligo would be maintained for a time longer than one hair cycle. See Applicant's amendment, pages 7-8. Applicant argues that the reliance on inherency is improper and that 'missing descriptive material is "necessarily present" not merely probable or possibly present in the prior art' citing *In re Newell* (top of page 9). Additionally, Applicant notes that the Tyr-A RNA-DNA is disclosed, however it is improper to

apply the property of a product to it use in a method claim. See pages 9-10. Finally, Applicant argues that the specification provides adequate disclosure for the breadth of the claims supporting the breadth of the claimed invention, and that the specification supports the unobvious contribution to the art. See pages 10-11. See Applicant's amendment pages 5-11. Applicant's arguments have been fully considered, but not found persuasive.

It is noted that claim 40 has been amended to indicate that the method steps previously recited result in an animal in which the genetic alteration results in a restoration of enzyme activity "lasting for more that one hair cycle and leading to development of dark pigmented hairs", however, there has been no amendment to the claim such that practicing the method as previously set forth specifically results in this new limitation. Examiner agrees that none of the references specifically teach that providing the Tyr-A RNA-DNA to the skin would result in the development of 'dark pigmented hair', however as noted previously this is not a consequence of practicing the method as presently claimed, rather, it is a consequence of the cell in the skin that is affected when practicing the method. Clearly, providing the Tyr-A RNA-DNA to any cell, *in vitro* or *in vivo* would result in a permanent alteration of the Tyr gene as demonstrated by the teaching and examples of Yoon *et al.* and Alexeev *et al.* Further, methods of delivering polynucleotide to the cells of the skin were known at the time of filing. At issue seems to be whether using methods known in the art for the delivery of a polynucleotide to the skin would have 'predictably' resulted in the genetic alteration of a hair follicle cell in the skin cell wherein the correction of the Tyr gene results in pigmentation of the hair from said follicle. Claim 40 is

directed to a method of correcting a mutation in skin cells *in vivo* comprising delivering the Tyr-A RNA-DNA RDO oligonucleotide to skin cells in an amount effective to cause stable genetic correction of the tyrosinase gene wherein the correction results in tyrosinase enzyme activity. Dependent claims recite two specific routes of delivery, topical application (claim 41) and intradermal injection (claim 42). Clearly, based on the claims as amended, the result of "lasting for more that one hair cycle and leading to development of dark pigmented hairs" would have resulted from practicing the method as previously claimed because none of the method steps have not been amended.

As summarized in the previous office action, at the time of filing Alexeev *et al.* teaches the RDO sequence Tyr-A RNA-DNA (see figure 1A) for the correction of the tyrosinase gene. Alexeev *et al.* teaches the RDO sequence Tyr-A RNA-DNA is effective in methods of delivery for altering the tyrosinase gene in primary melanocyte isolated from albino mice. Clearly, while practiced with cells were *in vitro*, the model system was designed to affect the TYR gene which affects albinoism *in vivo*. Alexeev *et al.* teaches and provides detailed guidance for several different reagents to optimize the delivery of the Tyr-A RNA-DNA to the cells and demonstrates the effective uptake of the oligonucleotide by the cells (page 1344, bridging first and second column and results in figures 2 and 3). Importantly, Alexeev *et al.* teaches that this sequence is effective in altering the endogenous tyrosinase gene and that after providing the Tyr-A RNA-DNA the tyrosinase enzyme activity is restored (see summary in abstract and figure 3). Moreover, Alexeev *et al.* teaches that other RDO sequences have been used effectively *in vitro*

and *in vivo* in methods to provide stable genetic changes in a gene of interest (page 1343, first column indicating the teachings of references 1-4, 10 and 11). Clearly, Alexeev *et al.* provide the necessary teaching to adapt the methods reduced to practice *in vitro* with an expectation to successfully practice the methods *in vivo*. Further, evidence that there is an expectation of success for the use of RDO sequences was provided by Yoon *et al.* (cited by Alexeev *et al.* as reference 1) who teaches methods of using a chimeric RNA-DNA oligonucleotide to target disease related mutations. More specifically, Yoon *et al.* teach that the methods disclosed demonstrate the feasibility of using chimeric RNA-DNA oligonucleotide in gene therapy protocols and specifically indicate that experimental results should be extended to therapeutic strategies in treating human diseases (page 2071, second column and page 2076, first column final paragraph). Like Alexeev *et al.* Yoon *et al.* provides the specific methodology and motivation for the delivery of a chimeric RNA-DNA oligonucleotide to a primary cell to correct a genetic disorder.

Examiner acknowledges that while each Alexeev *et al.* and Yoon *et al.* provide the materials and motivation necessary to practice the method as claimed, Yoon *et al.* fails to provide the specific methodology for affecting *in vivo* delivery known in the art at the time of filing. It is noted that the pending claims and upon review of the specification, that there is no specific delivery methodology set forth for specifically accomplishing the limitation of "lasting for more that one hair cycle and leading to development of dark pigmented hairs", and the teaching in the specification rely on the art for the practice of the delivery step. Furthermore, as noted above,

simply providing the Tyr-A RDO would appear to accomplish this limitation since the specific method steps have not been amended from the previous claims and in light of the lack of teaching in the specification for specific methodology.

Examiner would agree that neither Furth *et al.*, Gilchrest *et al.*nor Stout *et al.* specifically teach to use a Tyr-A RDO, however there is no specific methodology required for such delivery beyond that used for the delivery of any polynucleotide. As summarized previously, at the time of filing, various methods for the delivery of a polynucleotide to the skin were known. Furth *et al.* teach that polynucleotide can be delivered to the skin by (a & b) smearing of the polynucleotide onto an affected portion of the skin (topical application-claim 41), (c) intradermal inoculation (claim 42) and (d) interdermal inoculation (column 1, lines 37-45). Similarly, Stout *et al.* teach that various routes for delivery of a polynucleotide were known (column 1, lines 25-35), and specifically teach a method and device for the intradermal delivery to the skin by injecting a polynucleotide based medication into a subject (see figure 3 and 4 for device and column 2, lines 35-49). Gilchrest *et al.* teach and review specific methods for the topical application and delivery of polynucleotide to the skin to affect skin pigmentation (bridging columns 2-3). In summary, at the time of filing various methods for the delivery of a polynucleotide to the skin were known, and very specific methodology and devices had been developed to provide a polynucleotide to the skin of a subject. Though none of the references teach the use of a Tyr-A RDO, clearly all provide the necessary methodology for delivery that anticipate the delivery method step set forth in the claims as taught and supported in the

specification. Moreover, Gilchrest *et al* specifically teach that the methods of delivering polynucleotide can be used to change the pigmentation of skin.

Therefore, it is maintained that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the specific methodology known in the art for the delivery of a polynucleotide to the skin of a subject as taught by Furth *et al.*, Gilchrest *et al.* and Stout *et al.* for the delivery of the TyrA RNA-DNA to correct the tyrosinase gene as taught by Alexeev *et al.* Both Alexeev *et al.* and Yoon *et al.* specifically teach that chimeric RNA-DNA polynucleotide can be used for correcting gene mutations, and Yoon *et al.* specifically teaches that chimeric RNA-DNA polynucleotide should be adapted from the experimental models to protocols of gene therapy. Therefore, given the success of the methods for correcting the tyrosinase gene in primary skin cells through the use of the TyrA RNA-DNA polynucleotide as demonstrated by Alexeev *et al.*, and the specific teaching of Yoon *et al.* to use RNA-DNA polynucleotide in gene therapy protocols, one having ordinary skill in the art would have been motivated to use the specific methodology for the delivery of a polynucleotide to a skin cell known in the art as taught and exemplified by the teachings of Furth *et al.*, Gilchrest *et al.* and Stout *et al.* Alexeev *et al.* demonstrate the ability of the TyrA RNA-DNA polynucleotide to affect a genetic change in the tyrosinase gene in primary cells, therefore there would have been a reasonable expectation of success to practice the claimed method for correcting a mutation in the tyrosinase gene because both the methods of delivery and the method of affecting the tyrosinase gene were demonstrated to be effective at the time of filing.

Applicants arguments that the method as claimed is unobvious because of unexpected results is not persuasive because the material, motivation and expectation of success for changing various characteristics of the skin, in particular the pigmentation, were taught in the prior art. There is nothing particular about the methodology being claimed that would not be obvious as a whole in light of the teachings of the cited references. The TyrA RNA-DNA sequence was known and used to make permanent genetic changes in a cell from an albino animal model. Methods for the delivery of a polynucleotide to a skin to affect various cells and various characteristics of the skin were known and used at the time of the claimed invention. Examiner notes that the properties are subject to a product, not necessarily a method, however the TyrA RNA-DNA was use in a method and demonstrated to cause a genetic alteration the Tyr gene in cells from an albino animal. Thus, any result or outcome of using the RNA-DNA polynucleotide would be the same and would not represent an unexpected result. In contrast to the findings in *In re Chupp*, because the TyrA RNA-DNA disclosed in the art and taught in the specification are the same, the *Papesch* doctrine applied in *Chupp* would not apply because the rejection does not rely on structural similarities rather the product in use is the same (*ibid.* page 1439), and thus, the unobvious or unexpected advantageous properties are provided in the product disclosed in the art. Therefore, since the TyrA RNA-DNA disclosed in the specification and the prior art is the same, any property or affect of using the product would be expected.

With respect to the methodology for delivery providing the unexpected result, it is noted that claim 40 is broad encompassing any method of delivery to a skin cell, and on its face is not

commensurate in scope with the intradermal and topical methods of delivery taught in the present specification. As discussed in *In re Soni* the unexpected results must be commensurate in scope with the claims. Additionally, the courts have stated that "The evidence presented to rebut a *prima facie* case of obviousness must be commensurate in scope with the claims to which it pertains." (*In re Dill*, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979)). In the instant case, Examiner would agree that the breadth of a claim does not provide a basis or standard for expectation of success, however the instant claims do not provide any specific method of delivery and does not recite the specific parameters used to obtain the result indicated as 'unexpected' suing methods known in the art at the time of the claimed invention. Thus, with regard to the unexpected results Applicant argues are disclosed in the present specification, Applicant's arguments are not persuasive because the methods encompassed by claim 40 are not specifically drawn to the unexpected result pointed to by Applicant.

As noted previously, upon review of the specification it appears that it is neither the specific TyrA- RNA-DNA polynucleotide nor the delivery method that provides for affecting the result as claimed. It appears that what is being relied upon by Applicant as surprising is that a non-terminally differentiated cell or a cell which was less differentiated was reduced to practice in the instant specification. However, since the material and methods were known to practice the claimed invention, and the cited references provide motivation and expectation of success for practicing the method in vivo, Applicant's example for the reduction to practice of the claimed method is not found to be unexpected or surprising in light of the teaching of the cited references

as a whole. With respect to the newly added claims directed to animal models made by the above method, clearly a consequence of using the method would result in the non-human animal as claimed in particular as it is specifically directed to animal models of albinoism, alteration in the Tyr gene. With respect to other skin disorders and specific genes recited in the claims, as noted above Alexeev *et al.* teach that other RDO sequences have been used effectively *in vitro* and *in vivo* in methods to provide stable genetic changes in a gene of interest (page 1343, first column indicating the teachings of references 1-4, 10 and 11). Moreover, Alexeev *et al.* provide the necessary teaching to adapt the methods reduced to practice *in vitro* with an expectation to successfully practice the methods *in vivo*. Therefore, it would be obvious for any given gene associated with a particular disorder in the skin to be a gene of interest in an animal model. In light of the teachings of the references as a whole the claimed animal models made by the method of targeted gene alteration with an RDO would have obvious given the specific link between a mutation and any given skin disorder. Animal models for some of the genes were already known, and animal models made by different methods were known at the time of filing providing an expectation that alterations in these genes would result in the expected model.

Thus, it is maintained that the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40-42 stand and newly added claims 43-52 are provisionally rejected under the judicially created doctrine of double patenting over claims 1, 2, 8, 16-18 of copending Application No. 09/962,628. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Applicant argues that the allowability of the present claims has yet not been acknowledged and that it would be premature to file a Terminal Disclaimer at the time. Further, Applicants note the rejection contains reference to claims and a patent that is not related to the instant invention. See Applicant's amendment, bottom of page 11. Applicant's arguments have been fully considered but not found persuasive.

Initially, Examiner notes that the action contained information and discussion that was not material to the rejection of the pending claims. Examiner acknowledges that this was a typographical error and not relevant to the double patenting rejection, and apologizes for any confusion this may have caused.

However, with respect to Applicant's arguments regarding the indication of allowable subject matter, a provisional double patenting rejection can not be held in abeyance. The rejection is maintained because the subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter. With respect to newly added claims to the product produced by the claimed method, it is noted that the claimed animal model is the only product produced by the claimed method. Therefore, the product would be obvious in light of the method for producing such an animal. It is noted that the filing of a terminal disclaimer is not the only means to obviate an obvious double patenting rejection, and that abandonment of prosecution of copending claims would also obviate the provisional rejection.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

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